REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1 to 24 are pending with entry of this amendment. Claims 1, 17 and 21 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 21, support for negatively charged ring substituents can be found throughout the specification. For example, see specification at paragraphs 61 and 65.

With respect to amended claims 1 and 17, support for administration to individuals in need of immune response modulation and the range of immune response group members can be found throughout the specification. For example, see paragraph 33 of the specification.

Applicants submit that no new matter has been added to the application by way of the above amendment. Accordingly, entry of the amendment is respectfully requested.

The Election/Restriction Requirement.

In the Office Action of June 15, 2005, Applicants were requested to elect a single species of immune response and a single species of disclosed compound for current search and examination. The present Office Action reflects consideration of claims comprising the elected immune response species of NK cells and elected compound species of 6,6'-dithiodinicotinic acid. However, all of claims 1 to 24 remain pending and should ultimately be considered in the examination of this application.

Applicants note that, because claim 1 is an allowable generic claim and a claim linking all of the dependent claims 2-22, none of the claims should be considered withdrawn from prosecution in the present application but only considered species not currently under examination. Applicants note that the indicated withdrawn claim status should not be construed as abandonment or agreement with any particular position held by the Examiner in the Office Action.

35 U.S.C. §112, Second Paragraph.

Claim 21, was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the term "potentially" negative substituent was allegedly unclear. However, the issue is now moot due to the current amendment of claim 21.

35 U.S.C. §112, First Paragraph.

All claims currently under consideration (claims 1, 2, 5, 6, 10-12, and 17-24) were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Applicants traverse.

The Examiner argues that while the elected species are enabled, the specification allegedly "does not provide enablement for the modulation of *all* immune responses with *all* thione-forming disulfides." (Emphasis not added). Applicants note, however, that the ample specification does teach the claimed range of immune responses and thione-forming disulfides (TFDs).

The recitation of "thione-forming disulfides" is seen by the Examiner to allegedly be merely functional language. However, this is not the case. It is well established that the inventor can be his own lexicographer. The present specification describes TFDs as molecules in a class understood by those skilled in the art. For example, Applicants describe TFDs in broad generic, sub-generic and specific forms in the Thione-Forming Disulfides section of the specification (paragraphs 58-85). Thione-forming disulfides are disulfides that, upon reaction, for example with a thiol, give rise to a thione. The structures of disulfides prone to thione conversion are well known in the art, such as, e.g., disulfide molecules with electrophilic atoms beta to one or both a disulfide sulfurs. A typical thione-forming reaction sequence discussing and showing intermediate structures is presented in paragraphs 59 and 67. Subgeneric TFD structures of various types are presented in paragraphs 60 to 67. Specific preferred TFDs, including structures, formulas, extensive lists and references to a wide variety of TFDs of the invention are provided in paragraphs 68 to 85. One skilled in the art, in light of the specification, the general and specific structure and characteristics of TFDs described, and from the general meaning in the chemical arts, would be able to recognize TFD structures. The TFD term is clearly not "merely functional", but is well described in characteristic and structural terms.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. The

present rejections are based essentially on an allegation that undue experimentation would be required to practice the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See* In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *See id.*

Breadth of the Claims. The present claims are not unreasonably broad. The claims are confined to immune response modulation (a small subset of possible therapeutic and physiological effects of compounds). The claims are drawn to a specifically defined narrow group of compound structures (particular disulfides). The claim as a whole is doubly limited by the combination of these limitations.

Quantity of Experimentation. The quantity of experimentation necessary to practice the invention is minimal. Practice of, e.g., claim 1 by one skilled in the art does not require one to practice ***all*** embodiments of the claim at once or to succeed in every attempt, as is suggested by the Examiner's argument. "[D]isclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus posses the disclosed utility." See, *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). The specification provides numerous examples of administration of a TFD resulting in various forms of immune response modulation. The specification is replete with specific teaching of techniques to administer and detect such immune modulation. From this, the only experimentation left for one skilled would be to select one or more species of the method and follow the provided instructions. This is obviously routine.

Guidance. The amount of guidance provided in the present specification is quite high. Guidance is provided in a representative variety of modes of administration. For example, see the "Pharmaceutical Composition" and "Administration of Thione-Forming Disulfides" sections of the specification (paragraphs 86 to 106). Guidence in the exhaustive list of immune responses is backed up with practical methods of administering TFDs and detecting each type of immune response in combination with an exemplary TFD. For

example see, the sections entitled " Uses of Thione-Forming Disulfides in Immunomodulation" and "Immunomodulation in Treatment of Diseases and Other Ailments" (paragraphs 107 to 116).

The Examiner (page 4 of the Office Action) alleges that "Applicant discloses [only] disulfides bound to heterocycles comprising nitrogen β to the disulfide as the [TFDs] useful in the instant invention." However, this is not the case. It is well established that an enabling disclosure in a specification is not limited to the exemplary embodiments and the best mode disclosed. TFDs are generally described, e.g., at paragraph 59, and those of skill will understand what compounds, e.g., beyond dithiobis-heterocyclics, that will be subject to the chemistries described.

Working Examples. No working examples are required to provide an enabling disclosure (*Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302). However, here, a wide range of actual working examples (beyond the abbreviated list presented by the Examiner in the Office Action) is provided in the specification. For example, see Examples 1 to 13 in paragraphs 129 to 169. There is no legal case on record in which rejection was sustained in the face of even a fraction of the wide ranging and extensive actual examples provided in the present specification. Actual examples are presented for oral, injected and topical administration of TFDs. TFDs are administered to rodents, cats and humans. Modulated immune responses actually tested include, e.g., NK cell numbers, NK cell activity, splenocyte numbers, lymphoproliferation, CD3 cell counts, CD4 cell counts, CD8 cell counts, T cells, B cells, viral disease prophylaxis, neutrophils, macrophages and antibody titers. The heroic amount of actual examples provided, in light of the concepts and technical guidance in the specification strongly favor a finding of enablement.

State of the Art and Skill of Those in the Art. The state of skill in the art for the claimed invention is very high and this factor weighs heavily in favor of enablement. The Examiner states that the state of the art with regard to modulation of *all* immune responses is underdeveloped. Again, to practice the present invention, one does not need to practice all embodiments at once. One of skill, with an interest in a particular immune response, would be expected to practice that aspect of the invention without undue experimentation. One of

skill in another response could also practice the other aspect of the invention. Typically, there is not a need, desire or requirement to practice all aspects of the invention at once.

On page 6 of the Office Action, the Examiner suggests the present specification is inadequate for an alleged failure to disclose modulation of the innate immune system. The innate immune system is, e.g., immunity that is naturally present and is not due to prior sensitization. For example, innate immunity is well known to take the form of chemical and cellular systems not based on immune memory. The present specification describes modulation of a representative range of innate immune systems, e.g., modulation of NK cell activity, neutrophils and macrophages. See, e.g., the Examples section. This basis for rejection is faulty.

The state of the art associated with each type of response is very high. One skilled in the art could practice the claimed invention without extensive guidance. However, the present specification goes beyond the requirement by presenting theory and practice on how to modulate the full range of immune responses with TDFs.

Predictability of the Art. The Examiner bases an allegation of unpredictability solely on the statement that "the structure of those compounds is limited only by the function of the compounds." This is not the case, as discussed above. Based on the *Lilly* decision, cited by the Examiner, the thione-forming disulfides are more than adequately structurally described. One skilled in the chemical arts art would easily recognize and identify thione-forming disulfide compounds of the invention from the known disulfide associated structures conducive to formation of thione, and from guidance abundantly present in the specification. For instance, as described in the present specification and well known to those in the art, thione-forming disulfides typically have a structure with electrophilic atom (e.g., O, N, or S) present beta to at least one of the disulfide sulfurs. Members of the thione-forming disulfide genus are well known and support the predictability of the claims. The level of predictability, by those skilled in the art, for structures that are expected to be thione-forming, under particular conditions is very high.

Applicants find the Examiner's extensive arguments concerning the predictability of adverse drug interactions irrelevant to the present analysis. The present claims are directed to methods of modulating an immune response, not to methods that avoid drug-drug

interactions. The presence of embodiments of the invention wherein the therapeutic index is low does not make the claims unpredictable or unpatentable.

The specification provides evidence that immune response modulation by TFDs is predictable. Review of the Figures, Tables and Examples shows that the TFDs consistently provide immune response modulation across the full range of immune responses.

Because the weight of Wands factors tips heavily in favor of enablement for the current inventions, Applicants respectfully request withdrawal of the rejections.

35 U.S.C. §102.

Claims 1, 2, 5, 6, 10-12, and 17-24 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Henderson et al. (U.S. 6,001555) as evidenced by Toth et al., (J. Virology 67: 5879-88). Applicants traverse.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. In order for a reference to anticipate an invention, anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983). Here, Henderson does not expressly or inherently provide all limitations of the claims.

The present claim 1 reads as follows:

> 1. A method for modulating an immune response comprising administering to an individual in need an effective amount of a thione-forming disulfide;
>
> wherein the immune response is selected from the group consisting of: a cellular response, a humoral response and an innate immune response.

Henderson describes classes of compounds that inactivate retroviruses, such as HIV-1, by chemically attacking the CCHC zinc fingers of the viral nucleocapsid protein (abstract). This is completely unrelated to modulation of an immune response, as claimed, and does not inherently disclose the present invention.

The rejection is apparently based solely on the argument that administration of a TFD to "a patient for the treatment of HIV-1 will inherently, modulate the NK cells of said patient and effect said treatment of HIV-1." However, this is not necessarily the case, and therefore

the claimed limitations are not inherent in the prior art. "[T]he examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464, (1990; emphasis added). Because, for example, the missing limitation of modulating an immune response with TFDs is not necessarily present in the cited art, the rejection should be withdrawn.

For example, according to the Henderson reference itself, treatment of HIV-1 involves "attacking the CCHC zinc fingers of the viral nucleocapsid protein". However, it has not been shown that administration of TFDs at levels to inactivate virus in vivo by attacking zinc fingers necessarily would provide the effective amount needed for immune response modulation in the individual of the present claims. According to the holding of *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981), a rejection for alleged inherent anticipation can not be justified based on what would result due to optimization of conditions not necessarily present in the prior art. Therefore, the TFD application to *in vitro* cells in Henderson does not inherently provide the presently claimed methods of administering an effective amount of TFDs to an individual in need of immune modulation. The rejection must be withdrawn.

Toth does not provide the evidence of allegedly inherent TFD immune modulation in Henderson, as suggested by the Examiner (and necessary to the argument for rejection). In Toth the ability of NK cells to suppress HIV-1 replication was found related to their ability to produce alpha interferon (abstract). Again, this is unrelated to modulation of an immune response. For example, the "ability" of certain NK cells in Toth to produce IFN-α was not modulated, but constitutive. NK cells with an ability to produce IFN-α on infection with HIV correlated with reduced replication of HIV in that NK cell. This is not evidence that modulation of NK cells benefits HIV patients because, e.g., the NK cells of Toth are not modulated. The cited correlation of reduced HIV replication in NK cells with an ability produce IFN-α does not teach that modulation of NK killer activity must result from the TFD treatments of Henderson.

Because the cited art does not provide all the limitations of the claims, Applicant respectfully requests the rejections for alleged anticipation be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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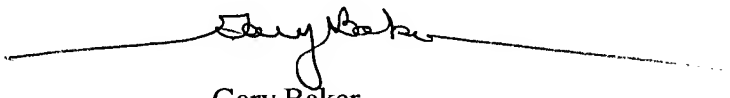
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for **1** month;
2) A transmittal sheet;
3) A fee transmittal sheet; and,
4) A receipt indication postcard.